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**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of

Douglas D. Ross et al.

Docket No: A9118

Appln. No.: 09/961,086

Group Art Unit: 1642

Confirmation No.: 6592

Examiner: S. Ungar

Filed: September 21, 2001

For: BREAST CANCER RESISTANCE PROTEIN (BCRP) AND THE DNA WHICH ENCODES IT

**DECLARATION UNDER 37 C.F.R. § 1.132**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Douglas D. Ross, hereby declare and state:

THAT I am a citizen of the United States of America;

THAT I have received the degrees of Doctor of Philosophy and Doctor of Medicine in Biochemistry and Medicine, respectively from Emory University, Atlanta, Georgia, in 1972 and 1974, respectively;

THAT I have been employed by the University of Maryland School of Medicine since 1982, where I currently hold a position as Professor of Medicine, with responsibility for conducting basic laboratory research in the area of molecular pharmacology, and clinical management of patients with cancer.

I understand that claims to antibodies that bind a polypeptide comprising the amino acid sequence of SEQ ID NO:1, included in the above-referenced U.S. patent application, have been

rejected. I further understand that the claims have been rejected because the Examiner believes that production of antibodies against a polypeptide described in Purnelle et al. (GenBank Accession No. P25371) or production of antibodies against a polypeptide described in Kirby et al. (GenBank Accession No. Q94960) would result in the production of an antibody that would also bind to the polypeptide of SEQ ID NO:1. I understand that the Examiner has based her position on the fact that the polypeptides of Purnelle et al. and Kirby et al. contain regions of five or more consecutive amino acids that share identity or homology with regions found in the polypeptide of SEQ ID NO:1. I understand that the Examiner believes one or more of these regions would be expected to comprise an antigenic determinant that would allow antibodies raised against the polypeptides of Purnelle et al. and Kirby et al. to cross-react with, and bind to, the polypeptide of SEQ ID NO:1.

I have reviewed the sequence alignments generated by the Examiner where portions of the amino acid sequences of the polypeptides of Purnelle et al. and Kirby et al. have been aligned with a portion of SEQ ID NO:1. A copy of these two documents are attached as Appendix 1 and 2, respectively. As stated by the Examiner, and as shown on the alignments, the Purnelle polypeptide only shares 30.5% identity with the polypeptide of SEQ ID NO:1, and the Kirby polypeptide only shares 32.1% identity with the polypeptide of SEQ ID NO:1.

I have also reviewed the alignments for regions of shared identity and homology. There are three regions of 100% identity between the polypeptide of Purnelle et al. and the polypeptide of SEQ ID NO:1 having five or more identical amino acids (regions with 5, 6 and 7 amino acids). There are four regions of 100% identity between the polypeptide of Kirby et al. and the

polypeptide of SEQ ID NO:1 having five or more identical amino acids (regions with 5, 5, 5 and 7 amino acids). Each of the seven regions are unique (i.e., there is no identity among the seven regions). These regions have been underlined on the alignments shown in Appendices 1 and 2.

1. Based on my review of the alignments, there are no large regions of homology between either the Purnelle et al. polypeptide and the polypeptide of SEQ ID NO:1, or the Kirby et al. polypeptide and the polypeptide of SEQ ID NO:1. While, as indicated above, there are some small, discrete regions of identity and homology, the overall alignments indicate that the polypeptides being compared are quite different in amino acid sequence. Further, there is no evidence that any of the polypeptides share conserved amino acids that would be required to form specific tertiary structures, such as cysteine residues that would form disulfide bonds, or alpha helices and beta sheets that would contribute to the three-dimensional structure of the protein. As a result, the three-dimensional confirmation that would be adopted upon folding of the three polypeptides would not be expected to result in any antigenic determinants in common between the three polypeptides.

Because there is no evidence of shared antigenic determinants, there would be no reasonable expectation that an antibody raised against either the Purnelle et at. polypeptide or the Kirby et al. polypeptide would be cross-reactive with, and to bind to, the polypeptide of SEQ ID NO:1.

2. Antibodies can be generated that recognize discreet, contiguous portions of a polypeptide. However, such regions of the polypeptide must be exposed on the surface of the polypeptide and they must be antigenic.

There is no indication in the documents cited by the Examiner that any of the three regions of the Purnelle et al. polypeptide having 100% identity with regions of the polypeptide of SEQ ID NO:1, or any of the four regions of the Kirby et al. polypeptide having 100% identity with regions of the polypeptide of SEQ ID NO:1, are exposed on the surface of the polypeptides. Nor is there any evidence that the regions of identity in the polypeptide of SEQ ID NO:1 are exposed on the surface of the polypeptide.

Further, based on antigenicity plots prepared for each of the seven regions (Appendices 3A-3C and 5A-5D), none of the regions appears to be highly antigenic. Indeed, a review of the overall antigenicity of the polypeptides of Purnelle et al. and Kirby et al. (Appendices 4A-4C and 6A-6B) indicates that none of the seven regions are among those regions that are highly antigenic and that would therefore be expected to serve as antigenic determinants when antibodies are being generated against the polypeptides.

As shown in Appendices 3A-3C, each of the regions of 100% identity highlighted in Appendix 1 (residues 551-557, 586-591, and 783-787) of the Purnelle et al. polypeptide has relatively low antigenicity. Appendices 4A-4C show the antigenicity of the entire Purnelle et al. polypeptide. Appendix 4A shows amino acids 1-360. Appendix 4B shows amino acids 361-720. Appendix 4C shows amino acids 721-1049. As can be seen from Appendices 4A-4C, the three regions of 100% identity are not among the regions of high antigenicity in the polypeptide.

Similarly, as shown in Appendices 5A-5D, each of the regions of 100% identity highlighted in Appendix 2 (residues 218-222, 242-248, 344-348 and 506-510) of the Kirby et al. polypeptide has relatively low antigenicity. Appendices 6A-6B show the antigenicity of the

entire Kirby et al. polypeptide. Appendix 6A shows amino acids 1-360. Appendix 6B shows amino acids 361-687. As can be seen from Appendices 6A-6B, the four regions of 100% identity are not among the regions of high antigenicity in the polypeptide.

As a result, there would be no reasonable expectation that antibodies would be generated against the regions of 100% identity noted for the polypeptides of Purnelle et al. and Kirby et al., or that even if such antibodies were generated, that they would bind to the polypeptide of SEQ ID NO:1.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: May 8, 2006

Douglas D. Ross